



(19)

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 846 693 A1

(12)

EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:

10.06.1998 Bulletin 1998/24

(51) Int. Cl.⁶: C07D 277/34, C07D 417/12,
A61K 31/425

(21) Application number: 96920002.1

(86) International application number:
PCT/JP96/01459

(22) Date of filing: 30.05.1996

(87) International publication number:
WO 96/38428 (05.12.1996 Gazette 1996/53)

(84) Designated Contracting States:

AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL
PT SE• KINOSHITA, Susumu
Minamisaitama-gun, Saitama 349-02 (JP)

• SATOH, Hiroya

Shimotsuga-gun, Tochigi 329-01 (JP)

• MURAKAMI, Koji,
Prescene Nogi Highlands 704
Tochigi 329-01 (JP)• TSUNODA, Masaki
Shimotsuga-gun, Tochigi 329-01 (JP)

(30) Priority: 02.06.1995 JP 159781/95

24.05.1996 JP 153139/96

(71) Applicant:

KYORIN PHARMACEUTICAL CO., LTD.
Chiyoda-ku, Tokyo 101 (JP)

(74) Representative:

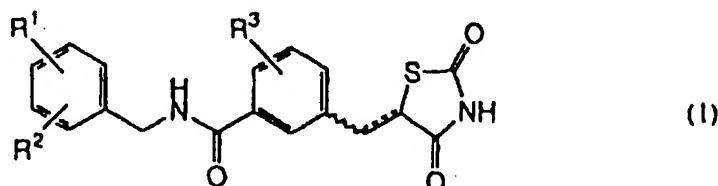
ter Meer, Nicolaus, Dipl.-Chem., Dr.
TER MEER STEINMEISTER & PARTNER GbR,
Patentanwälte,
Mauerkircherstrasse 45
81679 München (DE)

(72) Inventors:

- MAEDA, Toshio
Shimotsuga-gun, Tochigi 329-01 (JP)
- NOMURA, Masahiro
Shimotsuga-gun, Tochigi 329-01 (JP)
- AWANO, Katsuya
Oyama-shi, Tochigi 323 (JP)

(54) N-BENZYLIDIOXOTHIAZOLIDYL BENZAMIDE DERIVATIVES AND PROCESS FOR
PRODUCING THE SAME

(57) The present invention provides novel N-benzylidioxothiazolidylbenzamide derivatives that improve the insulin resistance and have potent hypoglycemic and lipid-lowering effects and processes for preparing the same, and relates to N-benzylidioxothiazolidylbenzamide derivatives characterized by being represented by a general formula (1)



EP 0 846 693 A1 [wherein R¹ and R² denote identically or differently hydrogen atoms, lower alkyl groups with carbon atoms of 1 to 4, lower alkoxy groups with carbon atoms of 1 to 3, lower haloalkyl groups with carbon atoms of 1 to 3, lower haloalkoxy groups with carbon atoms of 1 to 3, halogen atoms, hydroxyl groups, nitro groups, amino groups which may be substituted with lower alkyl group(s) with carbon atoms of 1 to 3 or hetero rings, or R¹ and R² link to form a methylenedioxy group, R³ denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen atom, and dotted line indicates double bond or single bond in combination with solid line], and processes for preparing the same.

Description**Technical field**

5 The present invention relates to novel N-benzylidioxothiazolidylbenzamide derivatives that improve the diabetes mellitus and the hyperlipidemia, and processes for preparing the same.

Background technologies

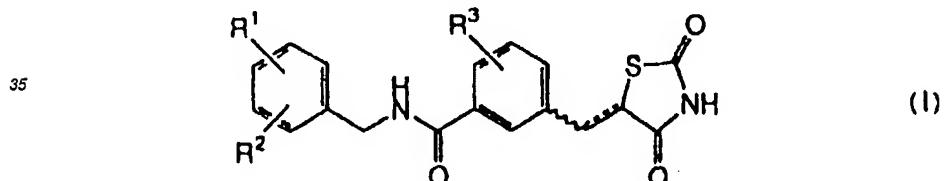
10 So far, as oral therapeutic drugs for diabetes mellitus, biguanide type and sulfonylurea type compounds have been used. However, with biguanide type compounds, lactic acidosis or hypoglycemia is caused and, with sulfonylurea type compounds, serious and prolonged hypoglycemia is caused, and the adverse effect thereof is posing a problem, hence the appearance of new therapeutic drug for diabetes mellitus without such defects is desired. It is also known that some of thiazolidine-2,4-dione derivatives exhibit hypoglycemic and lipid-lowering effects (Journal of Medicinal Chemistry, 15 Vol. 35, P. 1853 (1992), Published Unexamined Patent Application No. Hei 1-272573), but, in all of these compounds, the substituted position of middle benzene ring that connects thiazolidine-2,4-dione ring and aromatic ring is p-position, or the middle benzene ring has no substituent, further the aromatic ring of the former is oxazol ring, the linkage of the latter is through sulfonamide, and the like, which differ structurally from compounds of the invention, N-benzylidioxothiazolidylbenzamide derivatives.

20 For the non-insulin dependent diabetes mellitus (NIDDM) accounting for the majority of diabetics, a blood sugar-lowering drug that improves the insulin resistance and has high safety and effectiveness is strongly desired.

As a result of diligent studies on a drug that improves the insulin resistance and has potent hypoglycemic effects and high safety, the inventors have found that novel N-benzylidioxothiazolidylbenzamide derivatives represented by a following general formula (1) have excellent hypoglycemic and lipid-lowering effects, leading to the completion of the 25 invention.

Disclosure of the invention

Namely, the invention provides N-benzylidioxothiazolidylbenzamide derivatives represented by a general formula 30 (1)



40

[wherein R¹ and R² denote identically or differently hydrogen atoms, lower alkyl groups with carbon atoms of 1 to 4, lower alkoxy groups with carbon atoms of 1 to 3, lower haloalkyl groups with carbon atoms of 1 to 3, lower haloalkoxy groups with carbon atoms of 1 to 3, halogen atoms, hydroxyl groups, nitro groups, amino groups which may be substituted with lower alkyl group(s) with carbon atoms of 1 to 3 or hetero rings, or R¹ and R² link to form a methylenedioxy group, R³ denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen atom, and dotted line indicates double bond or single bond in combination with solid line], and their pharmaceutically acceptable salts.

The salts of compounds represented by the general formula (1) in the invention are of common use, and pharmaceutically acceptable metal salts such as alkali metal salts (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g. calcium salt, magnesium salt, etc.) and aluminum salt can be mentioned.

45

Moreover, the general formula (1) in the invention sometimes includes stereoisomers based on double bond and optical isomers based on thiazolidine portion. Such isomers and their mixtures are all to be included in the scope of this invention.

In the general formula (1) of the invention, for "lower alkyl group", straight or branched chain groups with carbon atoms of 1 to 4 such as methyl, ethyl, propyl and butyl are mentioned.

50

For "lower alkoxy group", straight or branched chain groups with carbon atoms of 1 to 3 such as methoxy, ethoxy and propoxy are mentioned.

For "lower haloalkyl group", straight or branched chain groups with carbon atoms of 1 to 3 such as trifluoromethyl are mentioned.

For "lower haloalkoxy group", straight or branched chain groups with carbon atoms of 1 to 3 such as trifluoromethoxy are mentioned.

For "halogen atom", fluorine atom, chlorine atom, bromine atom and iodine atom are mentioned.

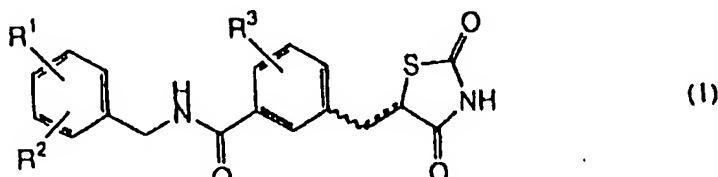
- 5 For "amino group which may be substituted with lower alkyl group", amino group, or methylamino group, ethylamino group, dimethylamino group, diethylamino group, etc., in which one or two hydrogen atoms are substituted with straight or branched chain lower alkyl group with carbon atoms of 1 to 3 such as methyl, ethyl and propyl, are mentioned.

According to the invention, compounds of said general formula (1) can be prepared through following processes.

Compounds of general formula (1) can be prepared by reacting compounds of general formula (7) with compounds of general formula (11).

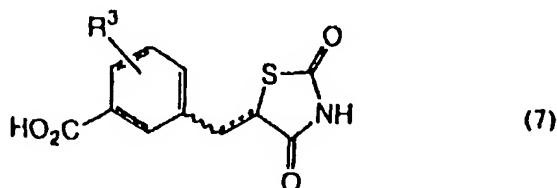
10

15



- 20 [wherein R^1 and R^2 denote identically or differently hydrogen atoms, lower alkyl groups with carbon atoms of 1 to 4, lower alkoxy groups with carbon atoms of 1 to 3, lower haloalkyl groups with carbon atoms of 1 to 3, lower haloalkoxy groups with carbon atoms of 1 to 3, halogen atoms, hydroxyl groups, nitro groups, amino groups which may be substituted with lower alkyl group(s) with carbon atoms of 1 to 3 or hetero rings, or R^1 and R^2 link to form a methylenedioxy group, R^3 denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen atom, and dotted line indicates double bond or single bond in combination with solid line]
- 25

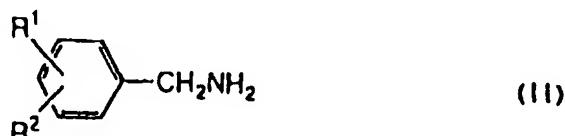
30



35

[wherein R^3 and dotted line are as described above]

40



45

[wherein R^1 and R^2 are as described above]

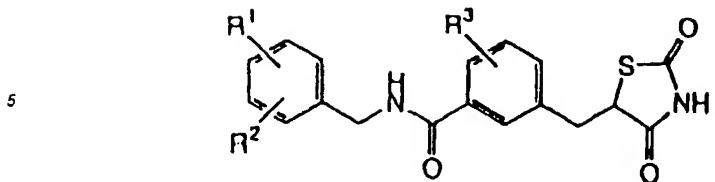
The reaction can be conducted by treating with condensing agent, for example, 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide, diethyl cyanophosphate or the like in an organic solvent, for example, dimethyl sulfoxide, N,N-dimethylformamide or the like. Moreover, if need be, an organic base, for example, triethylamine or the like may be added.

50

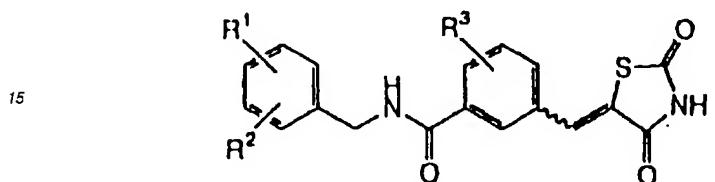
As the reaction temperature, ice cooling to room temperature can be used.

Compounds of general formula (1b) can be prepared by reducing compounds of general formula (1a).

55



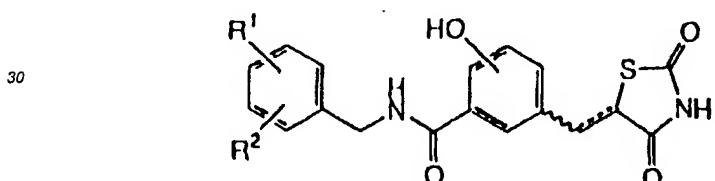
10 [wherein R¹, R² and R³ are as described above]



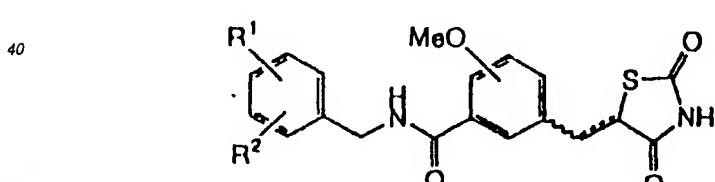
20 [wherein R¹, R² and R³ are as described above]

The reaction can be conducted by hydrogenating at ambient pressure to 4 kg/cm² in the presence of catalyst such as palladium/carbon in an organic solvent, for example, ethanol, ethyl acetate, N,N-dimethylformamide or the like or in a mixed solvent thereof at room temperature to heating. Or, it can be conducted by treating with sodium amalgam in an organic solvent, for example, alcohol such as ethanol or in a mixed solvent with water at room temperature to heating.

25 Compounds of following general formula (1d) can be prepared by reacting general formula (1c) with Lewis acid.



35 [wherein R¹, R² and dotted line are as described above]

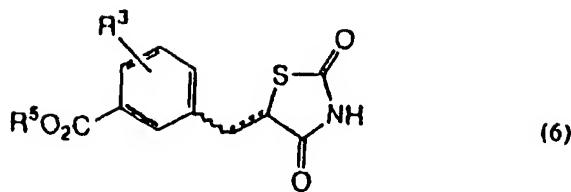


45 [wherein R¹, R² and dotted line are as described above]

The reaction can be conducted by treating with Lewis acid, for example, boron tribromide, boron trichloride or the like in an organic solvent, for example, dichloromethane, chloroform or the like at -78 °C to room temperature.

50 Compounds of general formula (7) can be prepared by hydrolyzing compounds of following general formula (6)

5



10

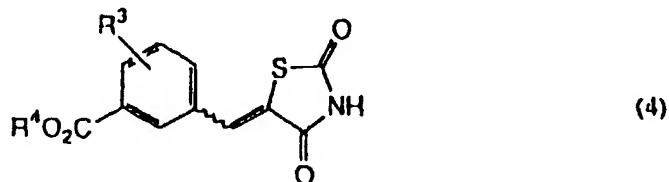
[wherein R³ and dotted line are as described above, and R⁵ denotes a lower alkyl group with carbon atoms of 1 to 3]

The reaction can be conducted under acidic or alkaline condition employing cooling to solvent refluxing as reaction temperature and, for example, refluxing under heat in a mixed solvent of acetic acid with concentrated hydrochloric acid is preferable.

15

Compounds of general formula (4) can be prepared by reacting compounds of following general formula (2) with compound of formula (3).

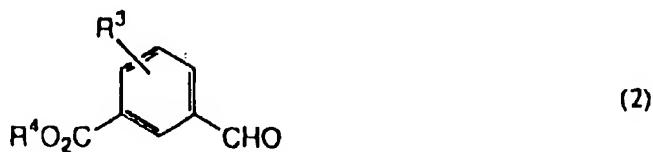
20



25

[wherein R³ is as described above, and R⁴ denotes a hydrogen atom or lower alkyl group with carbon atoms of 1 to 3]

30



35

[wherein R³ and R⁴ are as described above]

40



45

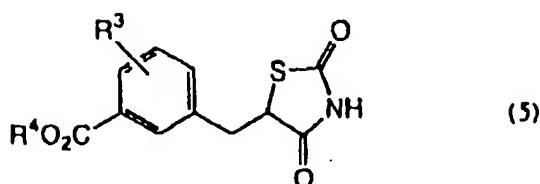
The reaction can be conducted in an organic solvent, for example, benzene, toluene, xylene or the like at room temperature to solvent-refluxing temperature as reaction temperature, but the solvent-refluxing temperature is preferable. Moreover, as a catalyst, addition of secondary amine (piperidine or the like) or acetic acid salt (ammonium acetate or the like) and acetic acid is suitable.

Also, it can be conducted by heating together with base (sodium acetate, piperidine or the like) without solvent.

Compounds of general formula (5) can be prepared by reducing compounds of general formula (4).

55

5



10

[wherein R³ and R⁴ are as described above]

The reaction can be conducted by hydrogenating at ambient pressure to 4 kg/cm² in the presence of catalyst such as palladium/carbon in an organic solvent, for example, ethanol, ethyl acetate, N,N-dimethylformamide or the like or in a mixed solvent thereof at room temperature to heating.

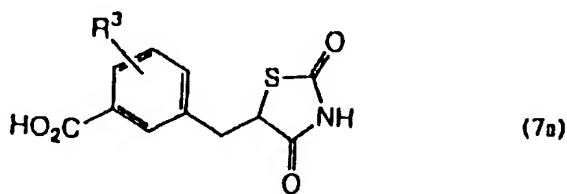
15

Or, it can be conducted by treating with sodium amalgam in an organic solvent, for example, alcohol such as ethanol or in a mixed solvent with water at room temperature to heating.

Compounds of general formula (7a) can be prepared by reacting compounds of following general formula (10) with thiourea, followed by hydrolysis.

20

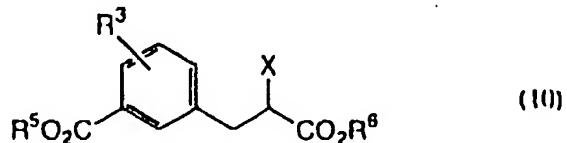
25



[wherein R³ is as described above]

30

35



[wherein R³ and R⁵ are as described above, R⁶ denotes a lower alkyl group with carbon atoms of 1 to 3, and X denotes a halogen atom]

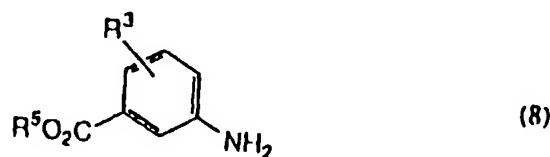
40

The reaction between compounds of general formula (10) and thiourea can be conducted in an organic solvent, for example, alcohol such as ethanol at room temperature to solvent refluxing temperature, but the solvent refluxing temperature is preferable. If need be, a base (sodium acetate or the like) may be added. Successive hydrolysis reaction can be conducted under acidic condition and, for example, it is preferable to reflux under heat in hydrochloric acid or in a mixed solvent of hydrochloric acid with organic solvent (sulforane or the like).

45

Compounds of general formula (10) can be prepared by converting compounds of general formula (8) to diazonium salts and then conducting Meerwein arylation with compounds of general formula (9).

50



55

[wherein R³ and R⁵ are as described above]



5

[wherein R⁶ is as described above]

The reaction can be conducted by diazotizing compounds of general formula (8) with nitrite such as sodium nitrite in an organic solvent, for example, alcohol such as methanol or ethanol, ketone such as acetone or methyl ethyl ketone 10 or water or in a mixed solvent thereof in the presence of hydrogen halide such as hydrochloric acid or hydrobromic acid, and then reacting with catalytic amount of cuprous salt such as cuprous oxide or cuprous chloride in the presence of compounds of general formula (9)

In following, the invention will be illustrated based on concrete examples, but the invention is not confined to these examples. The abbreviated terms used in examples represent following meanings.

15

¹ H NMR	Proton nuclear magnetic resonance spectrum
MS	Mass spectrum
CDCl ₃	Deuterated chloroform
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulfoxide
THF	Tetrahydrofuran
d ₆ -DMSO	Deuterated dimethyl sulfoxide

Example 1

25

Methyl 5-(2,4-dioxothiazolidin-5-ylidene)methyl-2-methoxybenzoate

A mixture of methyl 5-formyl-2-methoxybenzoate (490 mg), thiazolidine-2,4-dione (358 mg), ammonium acetate (401 mg), acetic acid (0.8 ml) and benzene (10 ml) was submitted to Dean-Stark dewatering apparatus to reflux for 4 hours under heat. After cooling, the crystals deposited were collected by filtration, washed with benzene and with 20 % aqueous solution of acetone, and then dried to obtain 634 mg (86 %) of aimed compound as crystals.

¹H NMR (d₆-DMSO), δ: 3.83(3H, s), 3.90(3H, s), 7.34(1H, d, J = 9.3Hz), 7.79(1H, s), 7.76-7.83(1H, m), 7.87-7.92(1H, m), 12.59(1H, s)

35

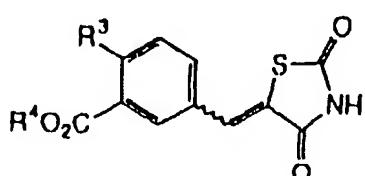
Examples 2 and 3

Similarly to Example 1, compounds in Table 1 were obtained.

40

[Table 1]

45



50

55

Example	R ³	R ⁴	Property	MS(m/z):M ⁺
5 2	EtO	Et	Crystal	—
3	i-PrO	H	Crystal	307

10

Example 4

15 Methyl 5-(2,4-dioxothiazolidin-5-yl)methyl-2-methoxy-benzoate

Methyl 5-(2,4-dioxothiazolidin-5-ylidene)methyl-2-methoxy-benzoate (9.52 g) was suspended into DMF (250 ml) and hydrogenated with 10 % palladium/carbon (10.0 g) at room temperature under a hydrogen pressure of 3.5 kg/cm². After the reaction, the solution was filtered and concentrated and water was added to the residue, which was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by means of silica gel column chromatography (developing solvent; methylene chloride:acetone = 50:1) to obtain 5.88 g (61 %) of aimed compound as an amorphous material.

25 MS(m/z):295(M⁺)

Example 5

5-(2,4-Dioxothiazolidin-5-ylidene)methyl-2-methoxy-benzoic acid

30 A suspension of methyl 5-(2,4-dioxothiazolidin-5-ylidene)-methyl-2-methoxybenzoate (629 mg) in acetic acid-concentrated hydrochloric acid (1:1, 18.0 ml) was refluxed for 6 hours under heat. After cooling, water (36 ml) was added and the crystals were collected by filtration, washed with water and dried to obtain 599 mg (100 %) of aimed compound as crystals.

35 ¹H NMR (d₆-DMSO), δ:3.89(3H, s), 7.31(1H, d, J = 8.8 Hz), 7.76(1H, dd, J = 2.4, 8.8Hz), 7.79(1H, s), 7.89(1H, d, J = 2.4Hz), 12.58(1H, s), 12.91(1H, br)

Example 6 and 7

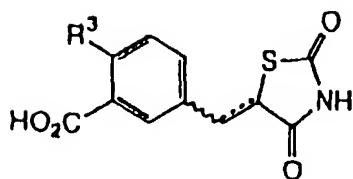
40 Similarly to Example 5, compounds in Table 2 were obtained.

45

50

55

[Table 2]



15

Example	R ³	Dotted line portion	Property	MS(m/z):M ⁺
6	MeO	Single bond	Crystal	—
7	Eto	Double bond	Crystal	293

20

25

Example 8

Methyl 2-bromo-3-(3-methoxycarbonyl-4-fluorophenyl)propionate

30 To a solution of methyl 5-amino-2-fluorobenzoate (4.12 g) in 47 % hydrobromic acid (11.4 ml), methanol (20 ml) and acetone (50 ml), a solution of sodium nitrite (1.88 g) in water (3 ml) was slowly added dropwise under cooling with salt-ice and stirring so as to keep an internal temperature of not higher than -5 °C. After stirred for 30 minutes as it was, ice bath was removed, methyl acrylate (13.3 ml) was added, and cuprous oxide (225 mg) was added little by little while stirring vigorously. After no nitrogen became to generate, the reaction liquor was concentrated under reduced pressure. The residue was dissolved into ethyl acetate, washed with water, saturated aqueous solution of sodium hydrogen carbonate and water in order, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by means of silica gel column chromatography (developing solvent; n-hexane:ethyl acetate = 10:1) to obtain 3.48 g (45 %) of aimed compound as an oily material.

35

40 ¹H NMR (CDCl₃), δ:3.25(1H, dd, J = 7.3, 14.6Hz), 3.46(1H, dd, J = 7.8, 14.2Hz), 3.75(3H, s), 3.93(3H, s), 4.38(1H, t, J = 7.8Hz), 7.09(1H, dd, J = 8.8, 10.8Hz), 7.38(1H, ddd, J = 2.4, 4.4, 8.8Hz), 7.80(1H, dd, J = 2.4, 6.3Hz)
MS(m/z):318, 320(M⁺)

45 Examples 9 and 10

Similarly to Example 8, compounds in Table 3 were obtained.

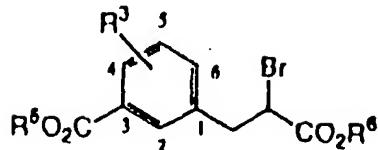
50

55

[Table 3]

5

10



15

20

25

Example	R ³	R ⁵	R ⁶	Property	¹ MS(m/z):M ⁺
9	6-MeO	Et	Me	Oily material	344
10	2-MeO	Me	Me	Oily material	330, 332

Example 11

30 5-(2,4-Dioxothiazolidin-5-yl)methyl-2-fluorobenzoic acid

To a solution of methyl 2-bromo-3-(3-methoxycarbonyl-4-fluorophenyl)propionate (1.22 g) in ethanol (40 ml), thiourea (356 mg) was added and the mixture was refluxed for 11 hours under heat. After cooling, this was concentrated under reduced pressure and water (50 ml) was added to the residue. After pH was adjusted to around 8 with saturated aqueous solution of sodium bicarbonate under stirring, ether (20 ml) and n-hexane (40 ml) were added, which was stirred for 10 minutes as it was. The crystals were collected by filtration, washed with water, and then dried. The solids thus obtained were dissolved into sulforane (10 ml) and, after 6N hydrochloric acid (20 ml) was added, the mixture was refluxed for 8 hours under heat. After cooling, this was poured into ice water and the crystals deposited were collected by filtration, washed with water, and then dried to obtain 403 mg (39 %) of aimed compound as crystals.

40

¹H NMR (d₆-DMSO), δ: 3.22(1H, dd, J = 8.3, 14.2Hz), 3.51(1H, dd, J = 4.4, 14.2Hz), 4.95(1H, dd, J = 4.4, 8.3Hz), 7.27(1H, dd, J = 8.3, 10.8Hz), 7.51(1H, ddd, J = 2.5, 4.9, 8.3Hz), 7.74(1H, dd, J = 2.5, 6.8Hz), 12.05(1H, s), 13.28(1H, s)
MS(m/z):269(M⁺)

45

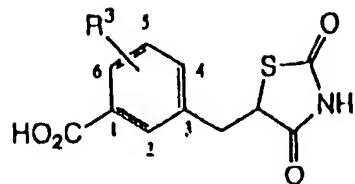
Examples 12 and 13

Similarly to Example 11, compounds in Table 4 were obtained.

50

55

[Table 4]



15

Example	R ³	Property	MS (m/z) : M ⁺
12	4-MeO	Crystal	281
13	2-Meo	Crystal	281

20

25

Example 14

N-(4-Trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-ylidene)methyl-2-methoxybenzamide

30 To a solution of 5-(2,4-dioxothiazolidin-5-ylidene)methyl-2-methoxybenzoic acid (1.00 g) and 4-trifluoromethylbenzylamine (627 mg) in DMF (10 ml), diethyl cyanophosphate (615 mg) and triethylamine (370 mg) were added at room temperature in an argon atmosphere under stirring, and the mixture was stirred for 5 hours as it was. The reaction liquor was poured into ice water and the crystals deposited were collected by filtration, washed with water, and then dried to obtain 1.31 g (84 %) of aimed compound as crystals. Further, these were recrystallized from ethanol to obtain purified aimed compound as yellow prismatic crystals. Melting point 210.0 ~ 211.5 °C

35

40

Elemental analysis (%): For C ₂₀ H ₁₅ F ₃ N ₂ O ₄ S			
	C	H	N
Calculated	55.04	3.46	6.42
Found	55.30	3.36	6.48

45

Examples 15 through 38

Similarly to Example 14, compounds in Table 5 and Table 6 were obtained.

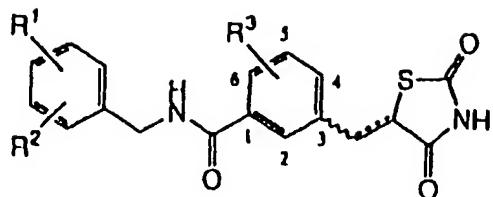
50

55

[Table 5]

5

10



15

20

25

30

35

40

45

50

55

Ex- ample	R^1	R^2	R^3	Dotted line portion	Melting point (°C) (Recrystallization solvent)	Composition formula	Elemental analysis (%)		
							C	H	N
15	H		6-MeO	Single bond	Amorphous	$C_{19}H_{18}N_2O_4S$	61.61	4.90	7.56
16	H		6-MeO	Double bond	2.09. 0 ~ 212. 0 (Suspended into hexane)	$C_{19}H_{16}N_2O_4S$	61.94	5.10	7.35
17	3-CF ₃		6-MeO	Single bond	1.45. 0 ~ 147. 0 (Ethy1 acetate- hexane)	$C_{20}H_{17}F_3N_2O_4S$	62.32	4.50	7.48
18	3-CF ₃		6-MeO	Double bond	1.88. 0 ~ 190. 0 (Ethanol)	$C_{20}H_{15}F_3N_2O_4S$	54.79	3.91	6.39
19	2-CF ₃		6-MeO	Single bond	1.79. 0 ~ 181. 0 (Ethy1 acetate- hexane)	$C_{20}H_{17}F_3N_2O_4S \cdot H_2O$	54.79	3.91	6.27
20	2-CF ₃		6-MeO	Double bond	1.97. 0 ~ 199. 0 (Ethanol)	$C_{20}H_{15}F_3N_2O_4S \cdot 1/4H_2O$	54.58	3.98	6.18
21	3, 5-CF ₃		6-MeO	Double bond	2.37. 0 ~ 239. 0 (DMF-ethanol)	$C_{21}H_{14}F_6N_2O_4S$	49.12	2.95	5.46
22	4-t-Bu		6-MeO	Single bond	1.35. 0 ~ 136. 0 (Ethy1 acetate- hexane)	$C_{23}H_{26}N_2O_4S \cdot 1/2H_2O$	64.77	6.14	6.57
23	4-t-Bu		6-MeO	Double bond	1.85. 0 ~ 188. 0 (Ethanol)	$C_{23}H_{24}N_2O_4S \cdot H_2O$	62.62	5.92	6.32
24	4-CF ₃ O		6-MeO	Double bond	1.66. 0 ~ 168. 0 (Ethanol)	$C_{20}H_{15}F_3N_2O_3S$	53.09	3.34	6.19
25	4-MeO		6-MeO	Double bond	2.09. 0 ~ 211. 0 (DMF-ethanol)	$C_{20}H_{18}N_2O_3S$	60.35	4.55	7.03
26	3, 4-MeO		6-MeO	Single bond	Amorphous	$C_{21}H_{22}N_2O_6S$	57.99	5.21	6.44
						$\cdot 1/4H_2O$	58.02	5.44	6.15

[Table 6]

Ex- example	R ¹ , R ²	R ³	Dotted line portion	Melting point (°C) (Recrystallization solvent)	Composition formula	Elemental analysis (%)		
						Calculated	Found	N
27	3, 4-methoxy-	6-MeO	Double bond	238. 0 ~ 241. 0 (DMF-ethanol)	C ₂₀ H ₁₆ N ₂ O ₆ S	58. 24	3. 91	6. 79
28	4-F	6-MeO	Single bond	Amorphous	C ₁₉ H ₁₇ FN ₂ O ₄ S • 1/2H ₂ O	57. 41	4. 56	7. 05
29	4-CF ₃	4-MeO	Single bond	204. 0 ~ 207. 0 (Acetonitrile)	C ₂₀ H ₁₇ F ₃ N ₂ O ₄ S	54. 79	3. 91	6. 39
30	3, 4-methoxy-	4-MeC	Single bond	134. 0 ~ 137. 0 (Methylene chloride)	C ₂₀ H ₁₈ N ₂ O ₆ S	57. 96	4. 38	6. 76
31	H	4-MeO	Single bond	95. 0 ~ 98. 0 (Ethanol)	C ₁₉ H ₁₈ N ₂ O ₄ S • 3/5H ₂ O	59. 85	5. 09	7. 35
32	4-CF ₃	2-MeO	Single bond	197. 0 ~ 199. 0 (Ethanol)	C ₂₀ H ₁₇ F ₃ N ₂ O ₄ S	54. 79	3. 91	6. 39
33	4-CF ₃	6-EtO	Double bond	227. 0 ~ 229. 0 (DMF-ethanol)	C ₂₁ H ₁₇ F ₃ N ₂ O ₄ S • 1/2H ₂ O	54. 90	3. 95	6. 10
34	3, 4-methoxy-	6-EtO	Double bond	213. 0 ~ 215. 0 (DMF-ethanol)	C ₂₁ H ₁₈ N ₂ O ₆ S	58. 99	4. 32	6. 70
35	4-CF ₃	6-i-PrO	Double bond	231. 0 ~ 232. 0 (Ethanol)	C ₂₂ H ₁₉ F ₃ N ₂ O ₄ S	56. 89	4. 12	6. 03
36	4-CF ₃	6-F	Single bond	145. 0 ~ 146. 0 (Methylene chloride)	C ₁₉ H ₁₄ F ₄ N ₂ O ₃ S	53. 52	3. 31	6. 57
37	4-(Me) ₂ N	6-MeO	Double bond	203. 0 ~ 208. 0 (Washed with ethanol)	C ₂₁ H ₂₁ N ₃ O ₄ S	53. 36	3. 22	6. 62
38	4-Me	6-MeO	Double bond	170. 0 ~ 172. 0 (Ethanol)	C ₂₀ H ₁₈ N ₂ O ₄ S	MS (m/z)	382 (M ⁺)	*

* ^1H NMR (d_6 -DMSO), δ : 2.86(6H, s), 3.94(3H, s), 4.38(2H, d, J = 5.9Hz), 6.69(2H, d, J = 8.8Hz), 7.18(2H, d, J = 8.8Hz), 7.28(1H, d, J = 7.9Hz), 7.74(1H, dd, J = 2,2,7.9Hz), 7.78(1H, s), 7.95(1H, d, J = 2.2Hz), 8.59(1H, t, J = 5.9Hz), 12.30(1H, br)

15 Example 39

N-(4-Trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-yl)methyl-2-methoxybenzamide

20 N-(4-Trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-ylidene)methyl-2-methoxybenzamide (500 mg) was suspended into ethanol (70 ml) and hydrogenated with 10 % palladium/carbon (500 mg) at room temperature under a hydrogen pressure of 3.0 kg/cm². The reaction liquor was filtered and concentrated and the residue was purified by means of silica gel column chromatography (developing solvent: methylene chloride:methanol = 50:1) to obtain 403 mg (80 %) of aimed compound as crystals. Further, these were recrystallized from ethyl acetate to obtain purified aimed compound as colorless powdery crystals. Melting point 176.0 ~ 177.5 °C

25

30

Elemental analysis (%): For $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_4\text{S}$			
	C	H	N
Calculated	54.79	3.91	6.39
Found	54.75	3.84	6.40

35

Examples 40 through 48

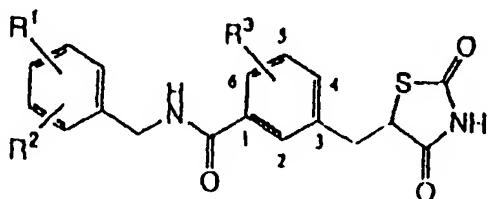
Similarly to Example 39, compounds in Table 7 were obtained.

40

[Table 7]

45

50



55

5
10
15
20
25
30
35
40
45
50
55

Ex- ample	R^1	R^2	R^3	Melting point (°C) (Recrystallization solvent)	Composition formula	Elemental analysis (%) Calculated/ Found		
						C	H	N
4.0	3. 5-CF ₃	6-MeO	6-MeO	167. 0 ~ 169. 0 (Ethanol)	C ₂₁ H ₁₆ F ₆ N ₂ O ₄ S	49. 80	3. 19	5. 53
4.1	4-Me	6-MeO	Amorphous		C ₂₀ H ₂₀ N ₂ O ₄ S	50. 00	3. 06	5. 54
4.2	4-CF ₃ O	6-MeO	Amorphous		C ₂₀ H ₁₇ F ₃ N ₂ O ₃ S	62. 48	5. 24	7. 29
4.3	4-MeO	6-MeO	Amorphous		C ₂₀ H ₁₉ N ₂ O ₃ S • 1/4H ₂ O	52. 86	3. 77	6. 17
4.4	3, 4-methyl- lenedioxy	6-MeO	Amorphous		C ₂₀ H ₁₈ N ₂ O ₆ S • 1/4H ₂ O	52. 68	3. 80	6. 45
4.5	4-(Me) ₂ N	6-MeO	Amorphous		C ₂₁ H ₂₁ N ₃ O ₄ S • 1/4H ₂ O	59. 31	5. 11	6. 92
4.6	4-CF ₃	6-EtO	159. 0 ~ 162. 0 (Ethanol)		C ₂₁ H ₁₉ F ₃ N ₂ O ₄ S • 1/4H ₂ O	59. 24	5. 03	6. 94
4.7	3, 4-methyl- lenedioxy	6-EtO	Amorphous		C ₂₁ H ₂₀ N ₂ O ₆ S	57. 33	4. 46	6. 69
4.8	4-CF ₃	6-i-PrO	158. 0 ~ 158. 5 (Ethyacetate- hexane)		C ₂₂ H ₂₁ F ₃ N ₂ O ₄ S	57. 10	4. 38	6. 89

Example 49

N-(4-Trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-yl)methyl-2-hydroxybenzamide

- 5 To a suspension of N-(4-trifluoromethylbenzyl)-5-(2,4-di-oxothiazolidin-5-yl)methyl-2-methoxybenzamide (800 mg) in anhydrous methylene chloride (30 ml), a 1.0N boron tribromidemethylene chloride solution (2.20 ml) was slowly added dropwise in an argon atmosphere under cooling with dry ice-acetone and stirring. After stirred for 6 hours at room temperature, the reaction liquor was allowed to stand for 3 days. After water was added and the mixture was stirred for 30 minutes, this was concentrated under reduced pressure. Ethyl acetate was added to the residue, which
10 was washed with water and then dried over anhydrous sodium sulfate. This was concentrated under reduced pressure and the residue was purified by means of silica gel column chromatography (developing solvent: methylene chloride:methanol = 40:1) to obtain 618 mg (80 %) of aimed compound as crystals. These were recrystallized from ethanol-water to obtain purified aimed compound as a light brown powdery crystals. Melting point 146.0 ~ 148.0 °C

15

20

Elemental analysis (%): For $C_{19}H_{15}F_3N_2O_4S$			
	C	H	N
Calculated	53.77	3.56	6.60
Found	53.92	3.88	6.49

25 Example 50

(-)-N-(4-Trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-yl)methyl-2-methoxybenzamide

- 30 Into 20 ml of ethyl acetate, 1.00 g of (\pm)-N-(4-trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-yl)methyl-2-methoxybenzamide obtained in Example 39 was dissolved under heat. After cooling, 0.276 g of L(-)-phenethylamine were added and the mixture was allowed to stand for a week at room temperature. The crystals deposited were filtered, washed with ethyl acetate and dried to obtain 0.753 g of L(-)-phenethylamine salt as white flaky crystals. Further, these were recrystallized from ethyl acetate to obtain 0.142 g of second crystals and 0.0908 g of third crystals. Melting point 191 ~ 193 °C, Optical rotation $[\alpha]_D = -87^\circ$ (C = 0.24, THF)

35

40

Elemental analysis (%): For $C_{28}H_{28}F_3N_3O_4S$			
	C	H	N
Calculated	60.10	5.04	7.51
Found	60.24	5.05	7.43

45

- To 20 ml of 1N hydrochloric acid, 0.753 g of first crystals were added under ice cooling. The mixture was stirred for 5 minutes and then filtered, and the crystals were washed with water and dried by heating. The crystals thus obtained were recrystallized from ethanol to obtain 0.532 g of aimed product as white powdery crystals. Melting point 194 ~ 195 °C, Optical rotation $[\alpha]_D = -100^\circ$ (C = 0.24, THF)

50

55

Elemental analysis (%): For $C_{20}H_{17}F_3N_2O_4S$			
	C	H	N
Calculated	54.79	3.91	6.39

(continued)

Elemental analysis (%): For C ₂₀ H ₁₇ F ₃ N ₂ O ₄ S			
	C	H	N
Found	54.72	3.90	6.35

5

For measuring the optical purity, part of crystals obtained (ca. 1 mg) was sampled and dissolved into 3 ml of methanol. After cooling, 0.2 ml of diazomethane-ether solution were added and, after stirred for 5 minutes at room temperature, solvent was distilled off under reduced pressure. Further, after distilled off the residual solvent for one hour with pump for distillation under reduced pressure, the residue was dissolved into methanol, and the optical purity was measured by means of liquid chromatography (column; chiral cell AD (Daicel), eluting solvent; hexane:isopropanol = 70:30, flow rate; 1.0 ml/min, measuring wavelength; $\lambda = 230$ nm, retention time; 22.31 min) to obtain 99.2 % ee.

15

Example 51

(+)-N-(4-Trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-yl)methyl-2-methoxybenzamide

20 Similarly to Example 50, 1.00 g of (\pm)-N-(4-trifluoromethylbenzyl)-5-(2,4-dioxothiazolidine-5-yl)methyl-2-methoxybenzamide obtained in Example 39 was submitted to the optical resolution with D(+)-phenethylamine to obtain 0.742 g of first crystals, 0.143 g of second crystals and 0.0587 g of third crystals as white flaky crystals for D(+)-phenethylamine salt. Melting point 191 ~ 193 °C, Optical rotation $[\alpha]_D = 87^\circ$ (C = 0.24, THF)

25

Elemental analysis (%): For C ₂₈ H ₂₈ F ₃ N ₃ O ₄ S			
	C	H	N
Calculated	60.10	5.04	7.51
Found	59.95	5.19	7.49

30

35 Similarly to Example 50, 0.742 g of first crystals were treated with 1N hydrochloric acid and recrystallized from ethanol to obtain 0.510 g of aimed product as white powdery crystals. Melting point 194 ~ 195 °C, Optical rotation $[\alpha]_D = 100^\circ$ (C = 0.24, THF)

40

Elemental analysis (%): For C ₂₀ H ₁₇ F ₃ N ₂ O ₄ S			
	C	H	N
Calculated	54.79	3.91	6.39
Found	54.88	4.03	6.42

45

For measuring the optical purity, N-methylation was made with diazomethane similarly to Example 50, and then the optical purity was measured by means of liquid chromatography (column; chiral cell AD (Daicel), eluting solvent; hexane:isopropanol = 70:30, flow rate; 1.0 ml/min, measuring wavelength; $\lambda = 230$ nm, retention time; 30.64 min) to obtain 99.2 % cc.

55

Employing inherited obese mice (C57BL ob/ob), the value of blood sugar was determined by collecting blood from caudal vein prior to testing. They were grouped so as not to cause any difference in the values of blood sugar, and the compounds of Example 36, 39, 46 and 48 were administered orally for 5 days at a dosage of 10 mg/kg, respectively.

For the glucose resistance test, 2 g/kg of glucose were administered orally after fasted overnight and the values of blood sugar at 0 minute, 30 minutes and 60 minutes were determined. The blood sugar-lowering rate was calculated from following formula.

$$\frac{[(\text{Sum of values of blood sugar of vehicle control group at 0, 30 and 60 minutes after administration of glucose}) - (\text{Sum of values of blood sugar of each group at 0, 30 and 60 minutes after administration of glucose})]}{(\text{Sum of values of blood sugar of vehicle control group at 0, 30 and 60 minutes after administration of glucose})} \times 100$$

Results are shown in Table 8. From these results, it was shown that the inventive compounds had potent hypoglycemic effects.

[Table 8]

Compound	Dosage (mg/kg)	Blood sugar-lowering rate (%)
Example 36	10	43
Example 39	10	47
Example 46	10	37
Example 48	10	45

Test example 2

Employing inherited obese mice (C57BL ob/ob), value of triglyceride in blood and value of free fatty acid in blood were determined by collecting blood from caudal vein prior to testing and they were grouped. After the compound of Example 39 was administered orally for 2 weeks at following dosages, the value of triglyceride in blood and the value of free fatty acid in blood were determined. The lowering rate of each parameter was calculated from following formula.

$$\frac{[(\text{value measured for vehicle control group}) - (\text{Value measured for each group of compound administration})]}{(\text{Value measured for vehicle control group})} \times 100$$

Results are shown in Table 9. From these results, it was shown that the inventive compound had potent lipid-lowering effects.

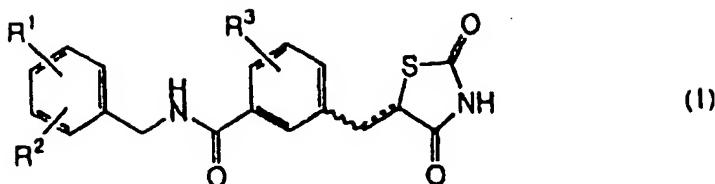
[Table 9]

Compound	Dosage (mg/kg)	Lowering rate of triglyceride in blood (%)	Lowering rate of free fatty acid in blood (%)
Example 39	1	28	26
	3	42	29

As above, with the N-benzylidioxothiazolidylbenzamide derivatives in accordance with the invention, drugs that improve the insulin resistance in the non-insulin dependent type diabetes mellitus and have potent hypoglycemic effects and high safety can be obtained.

Claims

- N-Benzylidioxothiazolidylbenzamide derivatives represented by a general formula (1)



10 [wherein R¹ and R² denote identically or differently hydrogen atoms, lower alkyl groups with carbon atoms of 1 to 4, lower alkoxy groups with carbon atoms of 1 to 3, lower haloalkyl groups with carbon atoms of 1 to 3, lower haloalkoxy groups with carbon atoms of 1 to 3, halogen atoms, hydroxyl groups, nitro groups, amino groups which may be substituted with lower alkyl group(s) with carbon atoms of 1 to 3 or hetero rings, or R¹ and R² link to form a methylenedioxy group, R³ denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen atom, and dotted line indicates double bond or single bond in combination with solid line], and their pharmacologically acceptable salts.

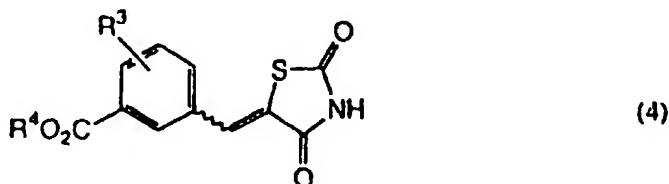
- 15
2. N-Benzylidioxothiazolidylibenzamide derivatives of Claim 1, one of compounds being N-(4-trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-yl)methyl-2-methoxybenzamide, and its pharmacologically acceptable salts.
 3. N-Benzylidioxothiazolidylibenzamide derivatives of Claim 1, one of compounds being N-(4-trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-yl)methyl-2-isopropoxybenzamide, and its pharmacologically acceptable salts.

25

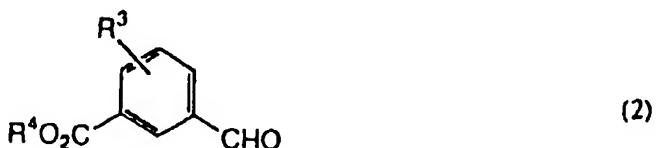
 4. N-Benzylidioxothiazolidylibenzamide derivatives of Claim 1, one of compounds being N-(4-trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-yl)methyl-2-ethoxybenzamide, and its pharmacologically acceptable salts.
 5. N-Benzylidioxothiazolidylibenzamide derivatives of Claim 1, one of compounds being N-(4-trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-yl)methyl-2-fluorobenzamide, and its pharmacologically acceptable salts.

30

 6. A process for preparing compounds represented by a general formula (4)

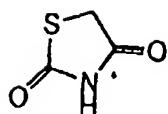


40 [wherein R³ denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen atom, and R⁴ denotes a hydrogen atom or lower alkyl group with carbon atoms of 1 to 3], characterized by reacting compounds represented by a general formula (2)



50 [wherein R³ and R⁴ are as described above], with compound represented by a general formula (3).

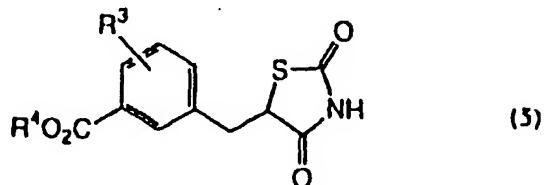
5



(3)

10 7. A process for preparing compounds represented by a general formula (5)

15

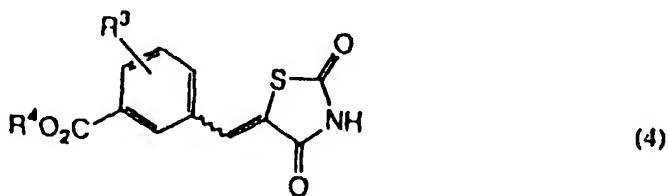


20

[wherein R³ denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen atom, and R⁴ denotes a hydrogen atom or lower alkyl group with carbon atoms of 1 to 3], characterized by reducing compounds represented by a general formula (4)

25

30



(4)

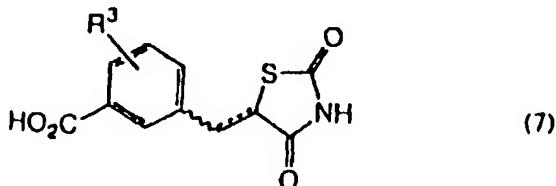
[wherein R³ and R⁴ are as described above].

35

8. A process for preparing compounds represented by a general formula (7)

40

45

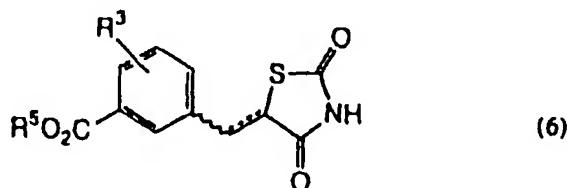


(7)

[wherein R³ denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen atom, and dotted line indicates double bond or single bond in combination with solid line], characterized by hydrolyzing compounds represented by a general formula (6)

50

55

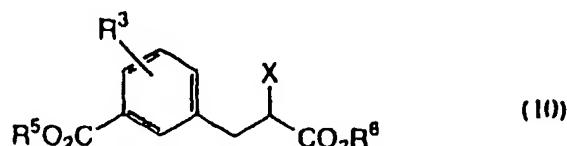


[wherein R³ and dotted line are as described above, and R⁵ denotes a lower alkyl group with carbon atoms of 1 to 3].

9. A process for preparing compounds represented by a general formula (10)

5

10

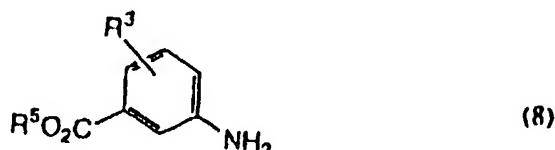


15

[wherein R³ denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen atom, R⁵ denotes a lower alkyl group with carbon atoms of 1 to 3, R⁶ denotes a lower alkyl group with carbon atoms of 1 to 3, and X denotes a halogen atom], characterized by converting compounds represented by a general formula (8)

20

25



25

[wherein R³ and R⁵ are as described above], to diazonium salts in the presence of hydrogen halide, and then reacting with compounds represented by a general formula (9)

30



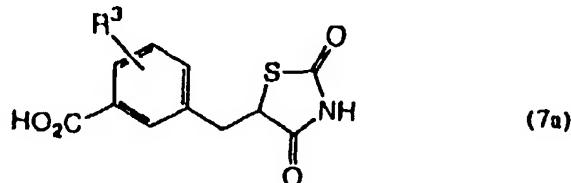
[wherein R⁶ is as described above].

35

10. A process for preparing compounds represented by a general formula (7a)

40

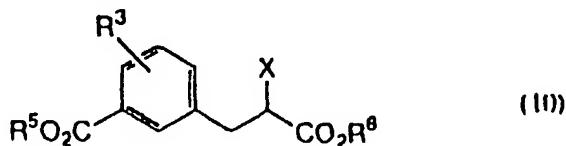
45



[wherein R³ denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen atom], characterized by reacting compounds represented by a general formula (10)

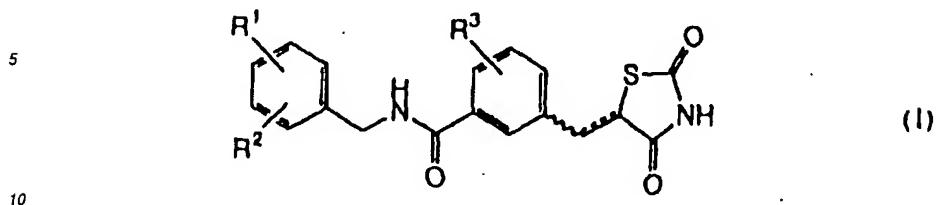
50

55

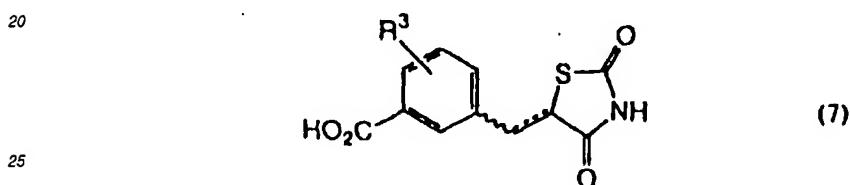


[wherein R³ is as described above, R⁵ denotes a lower alkyl group with carbon atoms of 1 to 3, R⁶ denotes a lower alkyl group with carbon atoms of 1 to 3, and X denotes a halogen atom], with thiourea, followed by hydrolysis.

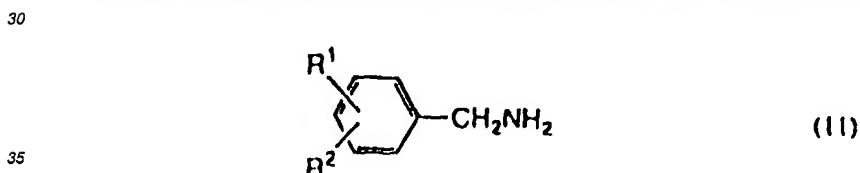
11. A process for preparing N-benzylidioxothiazolidylbenzamide derivatives represented by a general formula (1)



[wherein R¹ and R² denote identically or differently hydrogen atoms, lower alkyl groups with carbon atoms of 1 to 4, lower alkoxy groups with carbon atoms of 1 to 3, lower haloalkyl groups with carbon atoms of 1 to 3, lower haloalkoxy groups with carbon atoms of 1 to 3, halogen atoms, hydroxyl groups, nitro groups, amino groups which may be substituted with lower alkyl group(s) with carbon atoms of 1 to 3 or hetero rings, or R¹ and R² link to form a methylenedioxy group, R³ denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen atom, and dotted line indicates double bond or single bond in combination with solid line], characterized by reacting compounds represented by a general formula (7)

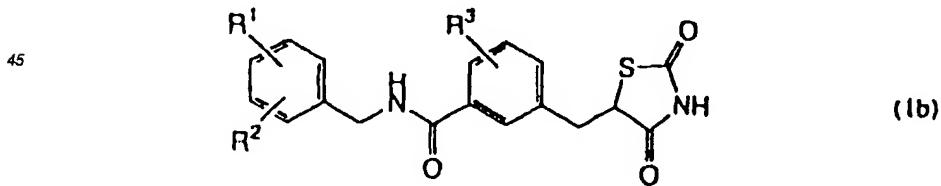


[wherein R³ and dotted line are as described above], with compounds represented by a general formula (11)

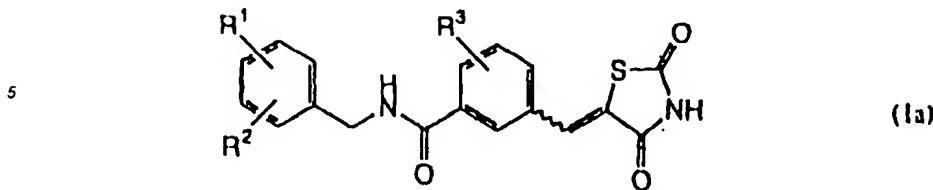


[wherein R¹ and R² are as described above].

12. A process for preparing N-benzylidioxothiazolidylbenzamide derivatives represented by a general formula (1b)

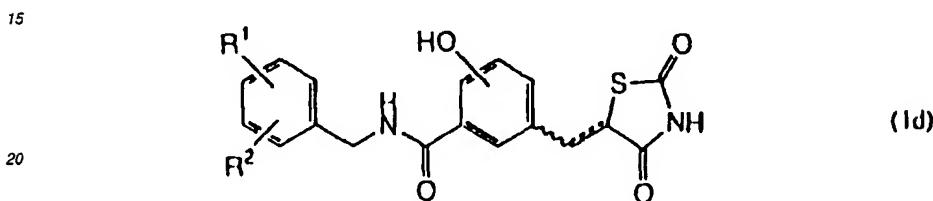


[wherein R¹ and R² denote identically or differently hydrogen atoms, lower alkyl groups with carbon atoms of 1 to 4, lower alkoxy groups with carbon atoms of 1 to 3, lower haloalkyl groups with carbon atoms of 1 to 3, lower haloalkoxy groups with carbon atoms of 1 to 3, halogen atoms, hydroxyl groups, nitro groups, amino groups which may be substituted with lower alkyl group(s) with carbon atoms of 1 to 3 or hetero rings, or R¹ and R² link to form a methylenedioxy group, and R³ denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen atom], characterized by reducing compounds represented by a general formula (1a)



10 [wherein R¹, R² and R³ are as described above].

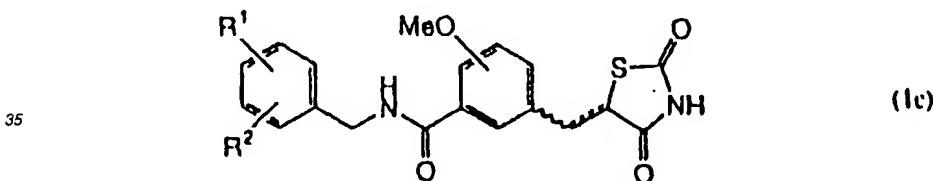
13. A process for preparing N-benzylidioxothiazolidylbenzamide derivatives represented by a general formula (1d)



20

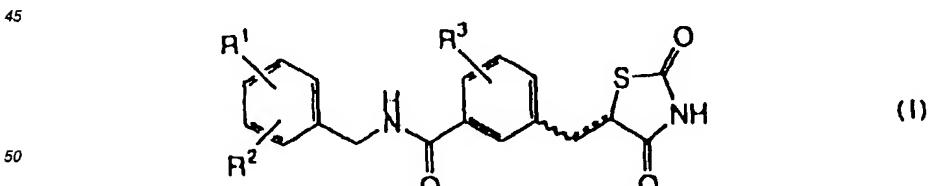
25 [wherein R¹ and R² denote identically or differently hydrogen atoms, lower alkyl groups with carbon atoms of 1 to 4, lower alkoxy groups with carbon atoms of 1 to 3, lower haloalkyl groups with carbon atoms of 1 to 3, lower haloalkoxy groups with carbon atoms of 1 to 3, halogen atoms, hydroxyl groups, nitro groups, amino groups which may be substituted with lower alkyl group(s) with carbon atoms of 1 to 3 or hetero rings, or R¹ and R² link to form a methylenedioxy group, and dotted line indicates double bond or single bond in combination with solid line], characterized by reducing compounds represented by a general formula (1c)

30



40 [wherein R¹, R² and dotted line are as described above], with Lewis acid.

14. A hypoglycemic agent having at least one kind of N-benzylidioxothiazolidylbenzamide derivatives represented by a general formula (1)



50

55 [wherein R¹ and R² denote identically or differently hydrogen atoms, lower alkyl groups with carbon atoms of 1 to 4, lower alkoxy groups with carbon atoms of 1 to 3, lower haloalkyl groups with carbon atoms of 1 to 3, lower haloalkoxy groups with carbon atoms of 1 to 3, halogen atoms, hydroxyl groups, nitro groups, amino groups which may be substituted with lower alkyl group(s) with carbon atoms of 1 to 3 or hetero rings, or R¹ and R² link to form a methylenedioxy group, R³ denotes a lower alkoxy group with carbon atoms of 1 to 3, hydroxyl group or halogen

EP 0 846 693 A1

atom, and dotted line indicates double bond or single bond in combination with solid line], and their pharmaco logically acceptable salts as effective component(s).

5

10

15

20

25

30

35

40

45

50

55

INTERNATIONAL SEARCH REPORT		International application No. PCT/JP96/01459												
A. CLASSIFICATION OF SUBJECT MATTER Int. Cl ⁶ C07D277/34, 417/12, A61K31/425														
According to International Patent Classification (IPC) or to both national classification and IPC														
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int. Cl ⁶ C07D277/34, 417/12, A61K31/425														
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched														
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE														
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; padding: 2px;">Category*</th> <th style="text-align: left; padding: 2px;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="text-align: left; padding: 2px;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">A</td> <td style="padding: 2px;">JP, 5-255288, A (Sankyo Co., Ltd.), October 5, 1993 (05. 10. 93) & EP, 549366, A1 & US, 5338855, A</td> <td style="padding: 2px;">1 - 14</td> </tr> <tr> <td style="padding: 2px;">A</td> <td style="padding: 2px;">JP, 5-213913, A (Adir et Co.), April 5, 1995 (05. 04. 95) & EP, 528734, A1 & US, 5266582, A & FR, 2680512, A1</td> <td style="padding: 2px;">1 - 14</td> </tr> <tr> <td style="padding: 2px;">A</td> <td style="padding: 2px;">JP, 1-272573, A (Pfizer Inc.), October 31, 1989 (31. 10. 89) & EP, 332331, A & US, 5061717, A</td> <td style="padding: 2px;">1 - 14</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	JP, 5-255288, A (Sankyo Co., Ltd.), October 5, 1993 (05. 10. 93) & EP, 549366, A1 & US, 5338855, A	1 - 14	A	JP, 5-213913, A (Adir et Co.), April 5, 1995 (05. 04. 95) & EP, 528734, A1 & US, 5266582, A & FR, 2680512, A1	1 - 14	A	JP, 1-272573, A (Pfizer Inc.), October 31, 1989 (31. 10. 89) & EP, 332331, A & US, 5061717, A	1 - 14
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
A	JP, 5-255288, A (Sankyo Co., Ltd.), October 5, 1993 (05. 10. 93) & EP, 549366, A1 & US, 5338855, A	1 - 14												
A	JP, 5-213913, A (Adir et Co.), April 5, 1995 (05. 04. 95) & EP, 528734, A1 & US, 5266582, A & FR, 2680512, A1	1 - 14												
A	JP, 1-272573, A (Pfizer Inc.), October 31, 1989 (31. 10. 89) & EP, 332331, A & US, 5061717, A	1 - 14												
<input type="checkbox"/> Further documents are listed in the continuation of Box C.		<input type="checkbox"/> See patent family annex.												
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed														
Date of the actual completion of the international search August 5, 1996 (05. 08. 96)		Date of mailing of the international search report August 13, 1996 (13. 08. 96)												
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.		Authorized officer Telephone No.												

Form PCT/ISA/210 (second sheet) (July 1992)